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Prior Caspofungin Exposure in Patients with Hematological Malignancies Is a Risk Factor for Subsequent Fungemia Due to Decreased Susceptibility in *Candida* spp.: a Case-Control Study in Paris, France▽

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Infections due to caspofungin-resistant *Candida* isolates in patients exposed to caspofungin therapy are increasing. We report here a nested case-control study which aimed at identifying factors associated with bloodstream infections caused by *Candida* spp. having reduced susceptibility to caspofungin (CRSC) in adults suffering from hematological malignancies. In univariate and multivariate analyses, infections with CRSC were associated with caspofungin exposure in the previous 30 days (odds ratio [OR] = 5.25; 95% confidence interval [95% CI], 1.68–16.35) and with an age of ≤65 years (OR = 3.27; 95% CI, 1.26–8.50).

Caspofungin is the first echinocandin approved for clinical use in France and has emerged as a major choice for primary treatment of invasive candidiasis and for empirical therapy in patients with persistent fever and neutropenia (4, 16). A growing number of breakthrough infections with *Candida* species that have low susceptibility to echinocandins have been reported for patients receiving echinocandin therapy (1, 3, 13, 17, 18, 20–22, 25). The *Candida parapsilosis* complex (i.e., *C. parapsilosis*, *C. metapsilosis*, and *C. orthopsilosis*) and *Candida guilliermondii* are intrinsically less susceptible than other *Candida* species to echinocandin due to naturally occurring point mutations in the *FKS* gene (6, 10, 19, 26). These point mutations were identified in clinical isolates having low susceptibilities to caspofungin, are clustered on two hot-spot regions (HS1 and HS2) (6, 10, 17, 19), and confer resistance to all three echinocandins (7, 18, 24). Recent epidemiological studies have reported concomitant increases in global caspofungin usage and in the incidence of *C. parapsilosis* fungemia (9, 23). We reported previously that the spectrum of species causing bloodstream infections (BSI) in patients who had been exposed to caspofungin differed significantly from that in BSI patients who had not been treated with this drug (15). Here, we explored whether recent prior exposure to caspofungin was associated with an increased risk of BSI with *Candida* spp. having reduced susceptibility to caspofungin (CRSC) in adults with hematological malignancies.

A matched case-control study was nested within the YEASTS program, an active surveillance program on yeast BSI implemented in the Paris area in France (5). The study population included patients >17 years of age suffering from hematological diseases and *Candida* BSI between 1 October 2002 and 1 February 2010. If several *Candida* BSI occurred in the same patient during the study period, only the episode due to CRSC—or the first episode if the caspofungin MICs were low—was considered in the analysis. Cases corresponding to mixed infection (with ≥2 species) were analyzed as a single infection due to the species for which the MIC was highest. Isolates were identified at the species level by phenotypic and/or molecular methods as described previously (15). *In vitro* caspofungin susceptibility was determined according to the EUCAST procedure (24) and tested in AM3 medium (6) as described previously (15). Sequencing of the hot-spot regions of *FKS* genes was performed for *C. albicans* and *C. glabrata* isolates for which caspofungin MICs were ≥0.5 mg/liter (17). Cases were patients with BSI due to (i) species known for their intrinsically low susceptibilities to caspofungin, i.e., the *C. parapsilosis* complex and *C. guilliermondii* (regardless of the caspofungin MICs) or to (ii) other *Candida* spp. for which MICs were ≥0.5 mg/liter (7). Controls were patients with BSI due to non-*C. parapsilosis* or -*C. guilliermondii* species for which caspofungin MICs were <0.5 mg/liter. Controls were randomly selected in a ratio of 2 per case and matched by center and a time period within 1 year. Patient information (sociodemographic data, the presence of underlying conditions, and histories of antifungal treatment with caspofungin or

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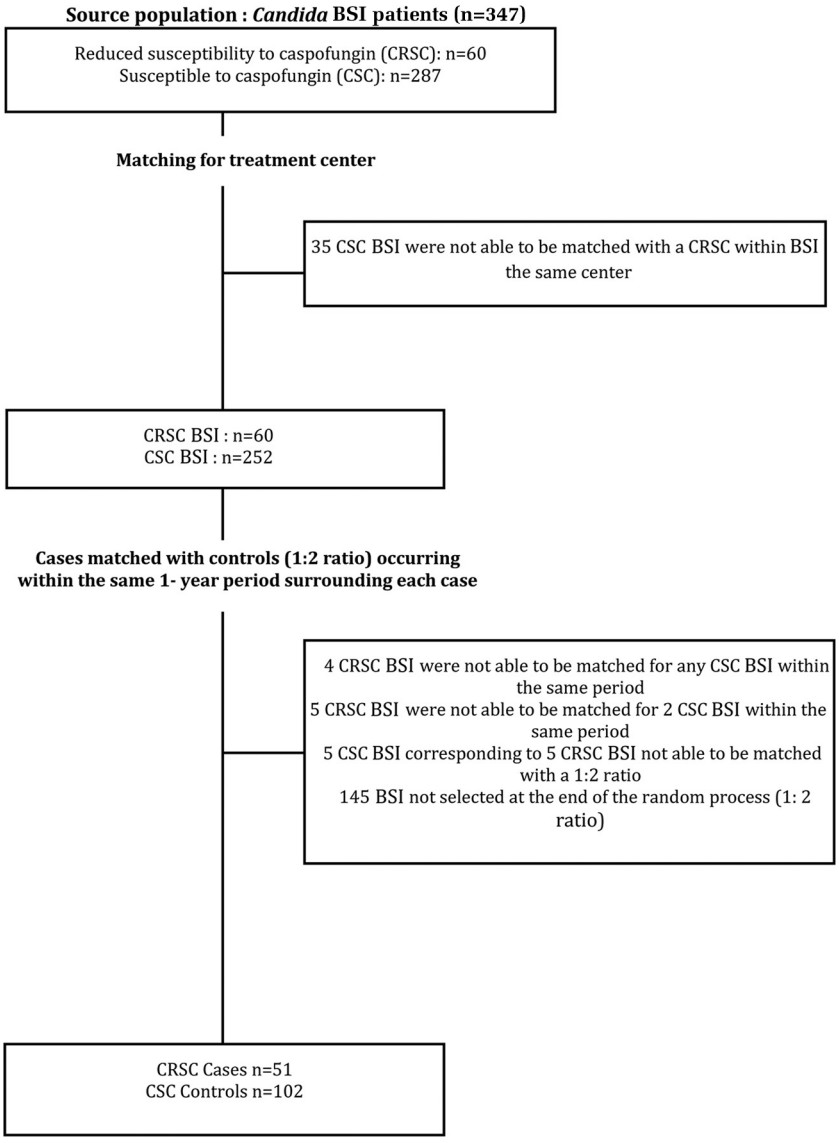

FIG. 1. Flow chart of the process used to match cases (infections with CRSC) with controls (infections with CSC) at a 1:2 ratio for cases and controls occurring within the same 1-year period.

with an azole antifungal in the 30 days prior to BSI) was also gathered. These data were systematically recorded within the framework of the YEASTS program at each center by either the microbiologist or the clinician, using a standardized anonymous questionnaire. Conditional logistic regression was used to estimate odds ratios (OR) and the associated 95% confidence intervals (95% CI) for univariate analysis (unadjusted OR) and multivariate analysis (adjusted OR). The final multivariate model was built through back stepwise elimination of variables of interest with the highest *P* value. *P* values of less than 0.05 for associations were considered to be statistically significant. Stata version 10.0 (StataCorp, College Station, TX) was used.

A total of 347 patients were eligible. The matching of two controls for each case by using treatment center and 1-year time period criteria led to a total of 153 patients (51 in the case group and 102 in the control group) being included in the study (Fig. 1). Of the 153 patients included in the study, 88 (57.5%) were male, and the median patient age was 48.0 years for the case group and 58.4 for the control group (Table 1). No patient had been exposed to any echinocandin other than caspofungin. The median MICs of caspofungin were 0.25 mg/liter for the case group (interquartile range [IQR] = 0.356) and 0.06 mg/liter for the control group (IQR = 0). *Candida* isolates identified in patients preexposed to caspofungin were *C. parapsilosis* and *C. guilliermondii* (accounting for 86.3% of the cases), as well as *C. albicans*, *C. glabrata*, *C. krusei*, and *C. lipolytica*. Point mutations in the *FKS* gene were identified in all *C. albicans* isolates ($n = 2$) and in one *C. glabrata* isolate.

In the univariate analysis, patients with CRSC isolates were more likely than those without CRSC isolates to be younger than 65 years ($P = 0.005$) and to have been exposed to caspofungin in the 30 days prior to BSI ($P = 0.001$) (Table 1). In the multivariate analysis, the risk of CRSC BSI was independently

TABLE 1. Univariate and multivariate analyses of factors associated with BSI caused by *Candida* spp. with decreased susceptibility to caspofungin in 153 adults suffering from hematological diseases[a]

Characteristic or parameter	No. (%) among case group (n = 51) or values for group	No. (%) among control group (n = 102) or values for group	Univariate analysis			Multivariate analysis		
			OR	95% CI	P	OR	95% CI	P
Sex			1.71	0.87–3.36	0.12			
Male	34 (66.7)	54 (52.9)						
Female	17 (33.3)	48 (47.1)						
Age at fungemia					**0.005**			**0.015**
≤65 years	45 (88.2)	66 (64.7)	3.81	1.51–9.57		3.27	1.26–8.50	
>65 years	6 (11.8)	36 (35.3)	1			1		
Median length (days) of stay[b] (IQR) in treatment center	15 (28.0)	14 (25.1)	1.01	0.98–1.03	0.51			
Prior exposure to caspofungin (within 30 days)	14 (27.5)	6 (5.9)	6.31	2.06–19.33	**0.001**	5.25	1.68–16.35	**0.004**
Prior exposure to azole antifungal agent (within 30 days)	5 (9.8)	12 (7.9)	0.81	0.27–2.46	0.71			
Presence of hematological disease(s):					0.09			
Acute leukemia	24 (47.1)	35 (34.3)	2.62	1.06–6.46				
Lymphoma	17 (33.3)	31 (30.4)	2.10	0.79–5.59				
Other(s)	10 (19.6)	36 (35.3)	1					
Presence of cancer	1 (2.0)	5 (4.9)	0.36	0.04–3.36	0.36			
History of:								
Previous surgery (<30 days)	2 (3.9)	11 (10.8)	0.36	0.08–1.64	0.19			
Allogeneic HSCT	10 (19.6)	12 (11.8)	1.87	0.74–4.75	0.19			
Autologous HSCT	4 (7.8)	4 (3.9)	2.00	0.50–8.00	0.33			
GVHD	6 (11.8)	6 (5.9)	2.50	0.67–9.31	0.17			
Use of or exposure to:								
Immunosuppressive agents (including corticosteroids)	14 (27.5)	28 (27.5)	0.86	0.40–1.85	0.69			
Broad-spectrum antimicrobial agents	25 (49.0)	56 (54.9)	0.72	0.32–1.60	0.42			
Central venous catheter	46 (90.2)	87 (85.3)	1.60	0.54–4.72	0.39			
Indwelling venous catheter	11 (21.6)	28 (27.5)	0.70	0.30–1.63	0.41			
Arterial catheter	3 (5.9)	11 (10.8)	0.55	0.15–1.96	0.35			
Urinary probe	5 (9.8)	12 (11.8)	0.81	0.27–2.46	0.71			
Other foreign material	3 (5.9)	7 (6.9)	0.86	0.22–3.32	0.82			
Death before day 30	15 (29.4)	40 (39.2)						

[a] HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host disease. Values in boldface indicate statistical significance.
[b] Values are available for 18 patients in the case group and 41 patients in the control group admitted for inpatient treatment.

higher in patients less than 65 years old than it was in older patients (OR = 3.27; P = 0.015) and in patients with prior exposure to caspofungin than in those without (OR = 5.25; P = 0.004) (Table 1). Thirty days after the onset of BSI, 15 patients in the case group (29.4%) and 40 in the control group (39.2%) had died.

We report a significant association between prior exposure to caspofungin and an elevated risk of CRSC BSI in adults with hematological malignancies. An association between prior exposure to an echinocandin, especially caspofungin, and CRSC BSI had been suspected previously, but earlier studies were hampered by limited numbers of patients and by the lack of a specific, case-control design (3, 11, 14, 22, 23). The incidence of *C. parapsilosis* BSI has been increasing over the past 6 years (8, 12), and this has been reported to correlate significantly with more prevalent caspofungin usage in some centers (9). Here, 44 cases of CRSC BSI (86.3%) were due to species whose susceptibility to caspofungin is intrinsically low. Similar to what has been strongly suspected in previous studies (15, 23), our main hypothesis is that the prevalent use of echinocandins is having a progressive ecologic impact, resulting in the selection in the gut or on the skin of *Candida* species with decreased (intrinsic or acquired) susceptibility to these drugs (2). However, fungal colonization prior to BSI could not be demonstrated here due to lack of recorded details. In conclusion, similar to previous exposure to azoles, recent exposure to caspofungin should be considered in prescribing initial treatment of *Candida* BSI in patients with hematological malignancies.

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